Low-dose aspirin is associated with reduced spontaneous preterm birth in nulliparous women

Maria Andrikopoulou, MD, PhD; Stephanie E. Purisch, MD; Roxane Handal-Orefice, MD, MPH; Cynthia Gyamfi-Bannerman, MD, MSc

BACKGROUND: Preterm birth is one of the leading causes of perinatal morbidity and mortality. Clinical data suggest that low-dose aspirin may decrease the rate of overall preterm birth, but investigators have speculated that this is likely due to a decrease in medically indicated preterm birth through its effect on the incidence of preeclampsia and other placental disease. We hypothesized that low-dose aspirin may also have an impact on the mechanism of spontaneous preterm labor.

OBJECTIVE: Our objective was to determine whether low-dose aspirin reduces the rate of spontaneous preterm birth in nulliparous women without medical comorbidities.

STUDY DESIGN: This is a secondary analysis of a randomized, placebo-controlled trial of low-dose aspirin for the prevention of preeclampsia in healthy, low-risk, nulliparous women. Low-risk women were defined by the absence of hypertension, renal disease, diabetes, other endocrine disorders, seizures, heart disease, or collagen vascular disease. Our study was limited to singleton, nonanomalous gestations. Women were eligible if they had prior pregnancy terminations but not prior spontaneous pregnancy loss <20 weeks. Current pregnancies that resulted in a loss or termination <20 weeks or antepartum stillbirth or had missing follow-up data were excluded. The treatment intervention was 60 mg of aspirin, initiated at 13–25 weeks' gestation or matching placebo. The primary outcome was spontaneous preterm birth <34 weeks' gestation. Secondary outcomes included spontaneous preterm birth <37 weeks and overall preterm birth <37 and <34 weeks. Baseline demographics and primary and secondary outcomes were compared between treatment groups. A logistic regression model was used to adjust for confounders related to spontaneous preterm birth.

RESULTS: Of 2543 included women, 1262 (49.6%) received low-dose aspirin and 1281 (50.4%) placebo. Baseline characteristics were similar between groups, except for marital status. The rate of spontaneous preterm birth <34 weeks was 1.03% (n = 13) and 2.34% (n = 30) in the low-dose aspirin and placebo group, respectively (odds ratio, 0.43, 95% confidence interval, 0.26–0.84). Additionally, the rate of spontaneous preterm birth <37 weeks was 6.58% (n = 83) in the low-dose aspirin group and 7.03% (n = 90) in the placebo group (odds ratio, 0.97, 95% confidence interval, 0.71–1.33), and the rate of overall preterm birth <37 weeks was 7.84% (n = 99) in the low-dose aspirin group and 8.2% (n = 105) in the placebo group (odds ratio, 0.97, 95% confidence interval, 0.72–1.31). After adjustment for variables that were clinically relevant or statistically significant, including body mass index, race, tobacco use, marital status, and education level, there was a significant reduction in spontaneous preterm birth <34 weeks in the low-dose aspirin group (adjusted odds ratio, 0.46, 95% confidence interval, 0.23–0.89). The rates of overall preterm birth <34 and <37 weeks and spontaneous preterm birth <37 weeks were similar in women who received low-dose aspirin compared with placebo.

CONCLUSION: Low-dose aspirin is associated with a substantial decrease in spontaneous preterm birth <34 weeks in healthy nulliparous women without comorbidities. These findings suggest a new therapeutic option for preterm birth prevention that requires further study.

Key words: low-dose aspirin, nulliparous, placental disease, platelet aggregation, preeclampsia, preterm birth, spontaneous preterm birth, uteroplacental ischemia

Preterm birth (PTB) is a challenging problem in obstetrics and one of the leading causes of perinatal morbidity and mortality, with the incidence reaching 9.6% in the United States.[1] Preterm births include both spontaneous deliveries that are preceded by preterm labor, preterm spontaneous rupture of membranes, or cervical insufficiency and account for approximately two-thirds of all PTBs. The remainder of preterm birth is iatrogenic or medically indicated.[2,3]

The pathophysiology of PTB remains multifactorial with infection or inflammation, uterine overdistention, or endocrine and immunological disorders playing important roles.[2] Uteroplacental ischemia and vascular disorders have also been shown to contribute in the pathogenesis of PTB.[4,5]

Low-dose aspirin has primarily been studied for the prevention of preeclampsia and fetal growth restriction.[6–14] Clinical data also suggest that low-dose aspirin may decrease the rate of overall PTB, but investigators have speculated that this is likely due to a decrease in medically indicated PTB.[15]

Clinical evidence suggests that low-dose aspirin may be a useful intervention for spontaneous PTB, but the data are either inconclusive or limited to special populations.[16–18] Silver et al[16] performed a secondary analysis of the Effects of Aspirin in Gestation and Reproduction trial and studied the association of low-dose aspirin (81 mg) with the risk of spontaneous PTB in women with a history of pregnancy loss.[16,17] They found an almost 50% reduction in the risk of spontaneous PTB in women who received low-dose aspirin compared with placebo (1.1% vs 2.2%), but this finding did not reach statistical significance (relative risk, 0.51, 95% confidence interval [CI], 0.19–1.34).

Also, a recent meta-analysis of 17 randomized controlled trials evaluating the risk of spontaneous PTB

Cite this article as: Andrikopoulou M, Purisch SE, Handal-Orefice R, et al. Low-dose aspirin is associated with reduced spontaneous preterm birth in nulliparous women Am J Obstet Gynecol 2017;xxx:xx-xx.

0002-9378/$36.00

https://doi.org/10.1016/j.ajog.2018.06.011


Click Supplemental Materials under article title in Contents at ajog.org

AJOG at a Glance

Why was this study conducted?
To determine whether low-dose aspirin reduces the rate of spontaneous preterm birth in nulliparous women without medical comorbidities.

Key findings
Low-dose aspirin is associated with a substantial decrease in spontaneous preterm birth <34 weeks in nulliparous women without medical comorbidities.

What does this add to what is known?
This study suggests a promising intervention that may decrease spontaneous preterm birth in an even broader population than previously reported, independent of preeclampsia.

in women taking low-dose aspirin-dipyridamol vs placebo for preeclampsia prevention showed that women at risk for preeclampsia assigned to antiplatelet treatment had a significantly lower risk of spontaneous PTB <37 and <34 weeks.[18] The authors concluded there was a benefit in reduction of spontaneous PTB in women at risk for preeclampsia.

Low-dose aspirin is well known for its antiinflammatory and platelet aggregation inhibition properties through cyclooxygenase inhibition. It is speculated that it may affect both the inflammatory and uteroplacental ischemia pathways of PTB, leading to the reduction of contractility and inflammation and thus reduction of spontaneous PTB.[19]

Given the burden of spontaneous preterm birth, the promising existing literature, and the availability, low cost, and biological plausibility of the intervention, our objective was to determine whether low-dose aspirin reduces the rate of spontaneous PTB in healthy nulliparous women with no medical comorbidities. We hypothesized that low-dose aspirin would lead to a reduction of spontaneous PTB.

Material and Methods

This is a secondary analysis of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units' randomized placebo-controlled trial of low-dose aspirin (60 mg) for the prevention of preeclampsia in women at low risk.[20] Women at low risk, defined by nulliparity and the absence of medical comorbidities, which included chronic hypertension, renal disease, diabetes mellitus, other endocrine disorders, seizures, heart disease, or collagen vascular disease, were eligible for the parent trial.

From 1989 to 1991, women between 13 and 25 weeks of gestation were enrolled from 7 clinical centers across the country. Women were randomized 1:1 to receive low-dose aspirin or placebo in an effort to assess the effect of low-dose aspirin on the incidence of preeclampsia and received treatment until delivery.

The primary outcome of the parent trial was incidence of preeclampsia, and investigators found no statistically significant difference between women who received aspirin compared with placebo.[20] PTB was a secondary outcome of the parent trial, and investigators did not find a difference in overall PTB by treatment assignment; however, spontaneous preterm birth was not assessed. Complete details of the study design and methods have been previously reported.[20] The study data are publicly available and deidentified and was therefore exempt from institutional review board review at our institution.

The current study focused on spontaneous preterm birth and was limited to singleton, nonanomalous gestations. Women were also eligible if a prior pregnancy was terminated at less than 20 weeks' gestation. Women with spontaneous pregnancy losses less than 20 weeks were excluded because we could not distinguish between those with prior first-trimester vs prior second-trimester losses in the data set, and those with prior second-trimester loss would have been at increased risk for spontaneous preterm birth.[21] Antepartum stillbirth or subjects with missing follow-up data were also excluded.

Women were then divided into 2 exposure groups based on their treatment assignment, low-dose aspirin vs placebo. The primary outcome was spontaneous PTB less than 34 weeks' gestation. PTB included both women with premature rupture of membranes or preterm delivery with intact membranes. Secondary outcomes included spontaneous PTB less than 37 weeks, overall PTB <37 and <34 weeks, amount of blood loss during delivery, postpartum hemorrhage, and placental abruption rates (diagnosed according to clinical findings [uterine tenderness and vaginal bleeding] or placental examination).

Maternal demographics, clinical characteristics, and primary and secondary outcomes were compared between the 2 groups. The χ^2 test was used for the analysis of categorical variables and Wilcoxon or Student *t* test for continuous variables, as appropriate. We fit a logistic regression model to adjust for confounders that were clinically related to spontaneous PTB or statistically different at baseline with a value of $P < .2$ (body mass index [BMI], race, tobacco use, marital status, and education level).

A sensitivity analysis was also performed excluding all cases of preeclampsia to eliminate the impact of preeclampsia on our outcomes. Level of significance for the primary outcome was set to a value of $P < .05$. All analyses were performed with SAS, version 9.4 (Cary, NC).

Results

Of 3171 subjects in the parent study, a total of 2543 women were included in this analysis. Details for excluded patients are listed in Figure 1. A total of 1262 (49.6%) received low-dose aspirin, and 1281 (50.4%) received placebo. Baseline characteristics were similar between groups, except for marital status (Table 1).

The rate of the primary outcome, spontaneous PTB <34 weeks, was 1.03%